発表した成果	発表者氏名	発表した場所	発表した時期	国内・外の別
基礎医学研究における漢方薬のエビデンス～抑肝散の精神神経症状に対する効果の検討～	宮田信吾	第14回愛媛東洋医学カンファレンス	2015	国内
ストレス応答系に対する抑肝散の効果	宮田信吾	第41回日本脳科学会	2014	国内

2．学会誌・雑誌等における論文掲載

掲載した論文	発表者氏名	発表した場所	発表した時期
精神神経科領域に対するKampoのエビデンス～治療抵抗性統合失調症に対する抑肝散の有用性に関する臨床研究から～.	宮岡　剛	医薬ジャーナル 51(2): 101-108	2015
Efficacy and safety of yokukansan in treatment-resistant schizophrenia: a randomized, double-blind, placebo-controlled trial (a Positive and Negative Syndrome Scale, five-factor analysis)	Tsuyoshi Miyaoka, Motohide Furuya, Jun Horiguchi, Rei Wake, Sadayuki Hashioka, Masaya Tohyama, Norio Mori, Yoshio Minabe, Masaomi Iyo, Shyuichi Ueno, Sachiko Ezoe, Kenta Murotani, Syuzo Hoshino, Haruo Seno	Psychopharmacology 232(1): 155-164	2015
Efficacy and Safety of Sansoninto in Insomnia with Psychiatric Disorder: An Open-Label Study.	Tsuyoshi Miyaoka, Kiminori Kawano, Motohide Furuya, Rei Wake, Sadayuki Hashioka, Kristian Liaury, Erlyn Limoa, Keiko Tsuchie, Michiyo Fukushima, Tomoko Araki, Jun Horiguchi	Journal Alternative & Integrative Medicine. (accept)	2014
Yokukansan increases serum Brain-derived neurotrophic factor (BDNF) levels in Gunn rat.	Motohide Furuya, Tsuyoshi Miyaoka, Sadayuki Hashioka, Rei Wake, Keiko Tsuchie, Jun Horiguchi	Journal of Brain Science 44	2014
治療抵抗性統合失調症に対する抑肝散の有効性.	宮岡　剛	臨床精神薬理 17(12): 1637-1643	2014
The Effects of Aging on Changes in Regional Cerebral Blood Flow in Schizophrenia.	Kazunori Kawakami, Rei Wake, Tsuyoshi Miyaoka, Motohide Furuya, Kristian Liaury, Jun Horiguchi	Neuropsychobiology 69(4): 202-209	2014
The effects of combine treatment of memantine and donepezil on Alzheimer's Disease patients and its relationship with cerebral blood flow in the prefrontal area.	Tomoko Araki, Rei Wake, Tsuyoshi Miyaoka, Kazunori Kawakami, Michiharu Nagahama, Motohide Furuya, Erlyn Limoa, Kristian Liaury, Sadayuki Hashioka, Kenta Murotani and Jun Horiguchi	International Journal of Geriatric Psychiatry 29(9): 881-889	2014

掲載した論文	発表者氏名	発表した場所	発表した時期
Minocycline improves recognition memory and attenuates microglial activation in Gunn rat: A possible hyperbilirubinemia-induced animal model of schizophrenia.	Kristian Liaury, Tsuyoshi Miyaoka, Toshiko Tsumori, Motohide Furuya, Sadayuki Hashioka, Rei Wake, Keiko Tsuchie, Michiyo Fukushima, Erlyn Limoa, Andi Jayalangkara Tanra, Jun Horiguchi	Progress in Neuro-Psychopharmacology & Biological Psychiatry 3; 50: 184-190	2014
(+)-Catechin protects dermal fibroblasts against oxidative stress-induced apoptosis.	Tanigawa T, Kanazawa S, Ichibori R, Fujiwara T, Magome T, Shingaki K, Miyata S, Hata Y, Tomita K, Matsuda K, Kubo T, Tohyama M, Yano K, Hosokawa K	BMC Complementary and Alternative Medicine 14(1): 133, 2014	2014
L-Arginine Stimulates Fibroblast Proliferation through the GPRC6A-ERK1/2 and PI3K/Akt Pathway.	Fujiwara T, Kanazawa S, Ichibori R, Tanigawa T, Magome T, Shingaki K, Miyata S, Tohyama M, Hosokawa K:	PLoS One 9(3): e92168	2014
Utility of Scalp Hair Follicles as a Novel Source of Biomarker Genes for Psychiatric Illnesses.	Maekawa M, Yamada K, Toyoshima M, Ohnishi T, Iwayama Y, Shimamoto C, Toyota T, Nozaki Y, Balan S, Matsuzaki H, Iwata Y, Suzuki K, Miyashita M, Kikuchi M, Kato M, Okada Y, Akamatsu W, Mori N, Owada Y, Itokawa M, Okano H, Yoshikawa T:	J Biol Psychiatry [Epub ahead of print]	2014
Exon resequencing of H3K9 methyltransferase complex genes, EHMT1, EHTM2 and WIZ, in Japanese autism subjects.	Balan S, Iwayama Y, Maekawa M, Toyota T, Ohnishi T, Toyoshima M, Shimamoto C, Esaki K, Yamada K, Iwata Y, Suzuki K, Ide M, Ota M, Fukuchi S, Tsujii M, Mori N, Shinkai Y, Yoshikawa T	Mol Autism 5(1): 49	2014
Serum microRNA profiles in children with autism.	Mundalil Vasu M, Anitha A, Thanseem I, Suzuki K, Yamada K, Takahashi T, Wakuda T, Iwata K, Tsujii M, Sugiyama T, Mori N	Mol Autism 5: 40	2014
Functional characterization of FABP3, 5 and 7 gene variants identified in schizophrenia and autism spectrum disorder and mouse behavioral studies.	Shimamoto C, Ohnishi T, Maekawa M, Watanabe A, Ohba H, Arai R, Iwayama Y, Hisano Y, Toyota T, Toyoshima M, Suzuki K, Shirayama Y, Nakamura K, Mori N, Owada Y, Kobayashi T, Yoshikawa T	Hum Mol Genet 23(24): 6495-511	2014

掲載した論文	発表者氏名	発表した場所	発表した時期
Zinc finger protein 804A (ZNF804A) and verbal deficits in individuals with autism.	Anitha A, Thanseem I, Nakamura K, Vasu MM, Yamada K, Ueki T, Iwayama Y, Toyota T, Tsuchiya KJ, Iwata Y, Suzuki K, Sugiyama T, Tsujii M, Yoshikawa T, Mori N	J Psychiatry Neurosci 39(5): 294-303	2014
N-ethylmaleimide-sensitive factor interacts with the serotonin transporter and modulates its trafficking: implications for pathophysiology in autism.	Iwata K, Matsuzaki H, Tachibana T, Ohno K, Yoshimura S, Takamura H, Yamada K, Matsuzaki S, Nakamura K, Tsuchiya KJ, Matsumoto K, Tsujii M, Sugiyama T, Katayama T, Mori N:	Mol Autism 5: 33	2014
【自閉症の分子基盤】自閉症の PET 研究について.	中村和彦, 鈴木勝昭, 尾内康臣, 辻井正次, 森　則夫	分子精神医学 14(2): 88-98	2014
Relationship between brain network pattern and cognitive performance of children revealed by MEG signals during free viewing of video.	Duan F, Watanabe K, Yoshimura Y, Kikuchi M, Minabe Y, Aihara K	Brain Cogn 86: 10-16	2014
Somatosensory evoked field in response to visuotactile stimulation in 3- to 4-year-old children.	Remijn GB, Kikuchi M, Shitamichi K, Ueno S, Yoshimura Y, Nagao K, Tsubokawa T, Kojima H, Higashida H, Minabe Y	Front Hum Neurosci 8	2014
Reduced long-range functional connectivity in young children with autism spectrum disorder.	Kikuchi M, Yoshimura Y, Hiraishi H, Munesue T, Hashimoto T, Tsubokawa T, Takahashi T, Suzuki M, Higashida H, Minabe Y	Soc Cogn Affect Neurosci	2014
A longitudinal study of auditory evoked field and language development in young children.	Yoshimura Y, Kikuchi M, Ueno S, Shitamichi K, Remijn GB, Hiraishi H, Hasegawa C, Furutani N, Oi M, Munesue T, Tsubokawa T, Higashida H, Minabe Y	Neuroimage 101: 440-447	2014
Unusual developmental pattern of brain lateralization in young boys with autism spectrum disorder: Power analysis with child-sized mabnetoencephalography.	Hiraishi H, Kikuchi M, Yoshimura Y, Kitagawa S, Hasegawa C, Munesue T, Takesaki N, Ono Y, Takahashi T, Suzuki M, Higashida H, Asada M, Minabe Y	Psychiatry Clin Neurosci	2015
Broader autism phenotype in mothers predicts social responsiveness in young children with autism spectrum disorders.	Hasegawa C, Kikuchi M, Yoshimura Y, Hiraishi H, Munesue T, Nakatani H, Higashida H, Asada M, Oi M, Minabe Y	Psychiatry Clin Neurosci	2014

掲載した論文	発表者氏名	発表した場所	発表した時期
Efficacy and safety of aripiprazole once-monthly in Asian patients with schizophrenia: A multicenter, randomized, double-blind, non-inferiority study versus oral aripiprazole.	Ishigooka J, Nakamura J, Fujii Y, Iwata N, Kishimoto T, Iyo M, Uchimura N, Nishimura R, Shimizu N	Schizophr Res 161(2-3): 421-8	2015
Association between serum levels of glial cell-line derived neurotrophic factor and attention deficits in schizophrenia.	Niitsu T, Shirayama Y, Matsuzawa D, Shimizu E, Hashimoto K, Iyo M	Neurosci Lett 575: 37-41	2014
A prospective comparative study of risperidone long-acting injectable for treatment-resistant schizophrenia with dopamine supersensitivity psychosis.	Kimura H, Kanahara N, Komatsu N, Ishige M, Muneoka K, Yoshimura M, Yamanaka H, Suzuki T, Komatsu H, Sasaki T, Hashimoto T, Hasegawa T, Shiina A, Ishikawa M, Sekine Y, Shiraishi T, Watanabe H, Shimizu E, Hashimoto K, Iyo M:	Schizophr Res 155(1-3): 52-8	2014
標準注意検査法がatomoxetine薬物治療による不注意症状の改善を反映しえた成人期注意欠如・多動性障害の一例.	河邉憲太郎, 堀内史枝, 妹尾香苗, 近藤静香, 竹之内美希, 小森憲治郎, 上野修一	臨床精神薬理 17: 1013-1023	2014
The Melatonin Receptor Agonist Ramelteon Effectively Treats Insomnia and Behavioral Symptoms in Autistic Disorder.	Kentaro Kawabe, Fumie Horiuchi, Yasunori Oka, Shu-ichi Ueno:	Case Reports in PsychiatryArticle ID 561071: 1-5	2014
愛媛大学医学部附属病院児童青年期精神科医療の現状とその変遷.	永井麻里奈, 河邉憲太郎, 近藤静香, 竹之内美希, 堀内史枝, 上野修一	最新精神医学 19: 339-346	2014
Comparison of Urinary Levels of 8-Hydroxy-2' deoxyguanosine between Young Females With and Without Depressive Symptoms during Different Menstrual Phases.	Tadayuki Iida, Ken Inoue, Yasuhiro Ito, Hiroaki Ishikawa, Miwa Kagiono, Ryoji Teradaira, Chiho Chikamura, Satoko Ezoe, Hiroshi Yatsuya:	Acta Medica Okayama (in press)	2014
Estimation of endoplasmic reticulum stress-inducing ability of nobiletin, a citrus polymethoxyflavonoid, in SK-N-SH human neuroblastoma cells.	Ikeda A, Miyata S, Yokosuka A, Mimaki Y, Ohizumi Y, Degawa M, Nemoto K:	Fundamental Toxicological Sciences 1(4): 169-172,	2014

厚生労働科学研究委託費
地域医療基盤開発推進研究「統合医療」に係る
医療の質向上・科学的根拠収集研究事業

自閉症スペクトラム障害に対する抑肝散の有用性の科学的知見の創出に関する研究

平成 26 年度　委託業務成果報告書

業務主任者　宮岡　剛

平成 27(2015)年 3 月

Ⅳ. 研究成果の刊行物・別刷

特集　臨床“Kampo”～各科領域におけるエビデンス～

7．精神神経科領域に対するKampoのエビデンス
～治療抵抗性統合失調症に対する抑肝散の有用性に関する臨床研究から～

宮岡　剛*

統合失調症は，精神疾患の中でも最も主要な疾患の一つである。現在，統合失調症の治療は，抗精神病薬による薬物療法が主流である。しかし，抗精神病薬による治療にも関わらず，病状が改善しない難治性や予後不良の治療抵抗性統合失調症の患者が約20～25%程度存在する。今後，新たな発想からの治療開発や治療戦略の必要性が指摘されている。抑肝散は，今や広く精神神経領域において用いられている。我々は治療抵抗性統合失調症への有用性をオープン試験で報告した。さらに，全国多施設共同の二重盲検ランダム化群間試験を実施し，抑肝散の効果の特徴について明らかにした。

本稿では，これらの臨床研究成果を示し，治療抵抗性統合失調症に対する抑肝散の有用性について述べる。その作用機序についても考察したい。

1．はじめに

抑肝散（yokukansan：YKS，yi-gan san：YGS，またはTJ-54）は，小児の癇癪や夜泣き，成人の不眠症に対して効果があるとされてきた生薬である[1]。近年，認知症患者に認められる精神ー行動障害（behavioral and psychological symptoms of dementia：BPSD）に対しての有効性に関する臨床研究の報告が，わが国を中心に増えている[2]。BPSDの症状には攻撃性亢進，焦燥，不穏，徘徊，幻覚や妄想等があり，これらは介護者にとって大きな負担となり，結果的には認知症患者の早期施設入所の主要な原因になっている。さらにBPSDは，患者自身のADL（activities of daily living）低下にも密接に関連していると考えられている。従って，BPSDを軽減することは非常に重要である。

これまでにBPSDに対して，抗精神病薬などによる治療介入について検討されてきたが，薬剤誘発性錐体外路症状（EPS）などの副作用が少なからず認められ，むしろ患者のADL低下を引き起こす恐れがあるという問題があった[3]。岩崎らは，抑肝散がBPSDに対して有効であり忍容性に優れているとする臨床研究結果を初めて報告した[2]。その後もBPSDに対する抑肝散の有効性に関する臨床研究の報告が，引き続きなされている。

我々は，抑肝散のBPSDに対する優れた治療的有効性と忍容性を有することを参考にし，いくつかの精神疾患に対する治療有効性と忍容性について検討を行った。その中でも，境界人格障害（borderline personality disorder：BPD）[4]，抗精神病薬誘発性の遅発性ジスキネジア（tardive dyskinesia：TD）[5]，感覚遮断による幻覚現象[6]，

*島根大学医学部精神医学講座・准教授（みやおか・つよし）

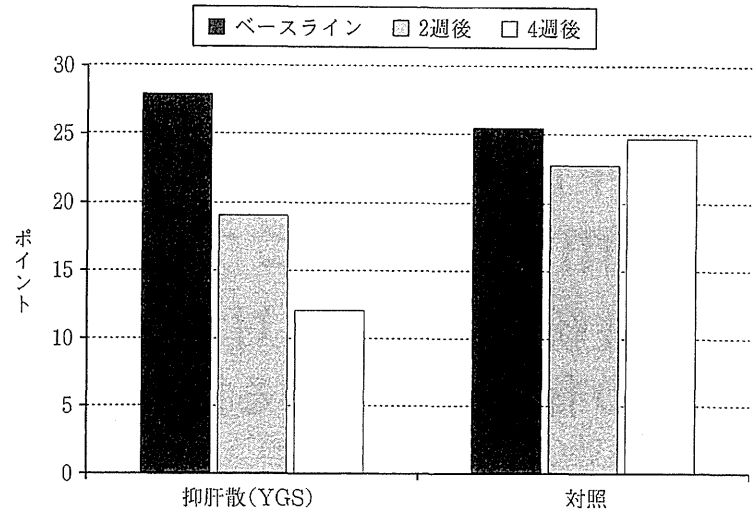

図1 PANSS 陽性尺度
抑肝散（YGS）の追加投与により，精神症状の有意な改善を認めた．
PANSS：Positive and Negative Syndrome Scale
（文献 10 より）

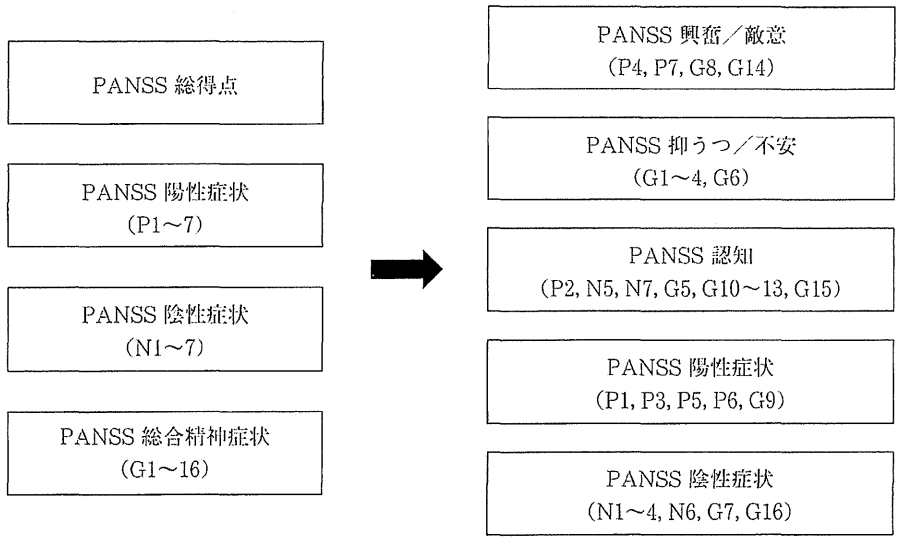

図2 PANSS 5 因子解析
抑肝散の効果の詳細な特徴を明らかにするため，PANSS 5 因子解析を行った．
PANSS：Positive and Negative Syndrome Scale （文献 16 より）

遅発性統合失調[7]，自閉症スペクトラム障害[8)9)]，そしてオープン試験のデザインで治療抵抗性統合失調症[10]に対する抑肝散の有効性と忍容性に関する臨床研究を既に報告した。平成 22 ～ 24 年（2010 ～ 2012 年）の期間において，"厚生労働科学研究費補助金―医療技術実用化総合研究事業―" として，『治療抵抗性統合失調症に対する抑肝散の有用性と安全性に関する多施設共同二重盲検

BPSD：behavioral and psychological symptoms of dementia（精神－行動障害）
EPS：錐体外路症状，BPD：borderline personality disorder（境界人格障害）
TD：tardive dyskinesia（遅発性ジスキネジア）

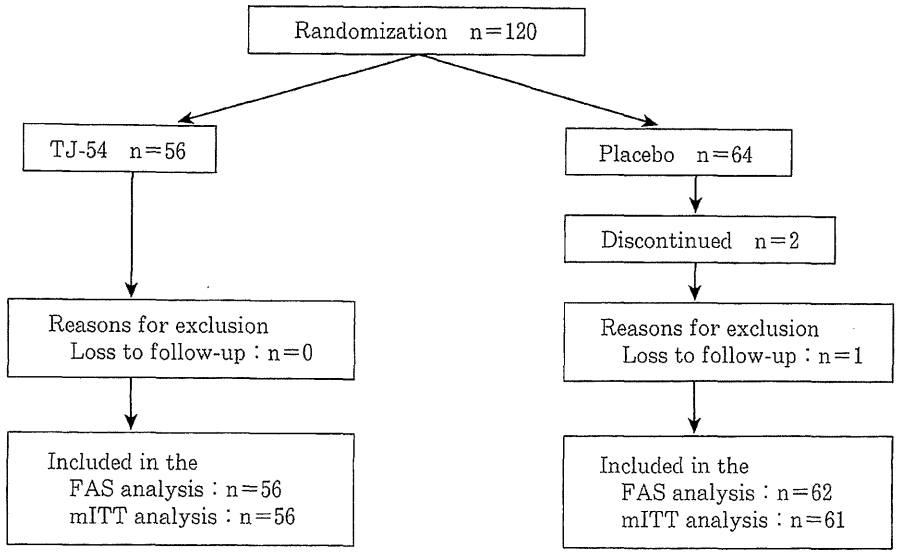

図3　研究フローチャート

120例の登録された患者のうち，脱落した症例は，プラセボ群の3例であった．
TJ-54：抑肝散

（筆者作成）

ランダム化比較試験』を実施した。その結果から，抑肝散が治療抵抗性統合失調症に対して優れた治療効果を有する可能性があることが推察された[11]。よって本稿では，これまでの臨床研究報告を紹介し，その作用機序については基礎研究の結果を加えて考察する。

2．治療抵抗性統合失調症に対する有効性～オープンラベル試験～

統合失調症は生涯罹患率が約0.8%であり，精神疾患の中でも最も主要な疾患の一つである。1950年代に抗精神病薬が開発されて以来，統合失調症の治療は抗精神病薬による薬物療法が主流となっている。さらに近年，非定型抗精神病薬が開発され，その有効性が期待されていた。しかし，現在においても抗精神病薬による治療にも関わらず，病状が改善しない難治性や，予後不良の治療抵抗性統合失調症患者が約25%存在するのも事実である[12]。治療抵抗性統合失調症に対する薬物治療は非常に困難であり，主剤以外の向精神薬の追加投与が必要となり，結果として統合失調症患者に対して多剤大量の向精神薬を投与することになり，さまざまな有害事象を引き起こす原因となる。このことは，統合失調症治療における抗精神病薬の限界を示唆するものであり，今後，新たな薬物療法の開発が待たれる。そこで我々は，治療抵抗性統合失調症の治療に抑肝散が応用可能であるかを検討した[10]。

1）対象と方法

対象症例は，DSM-Ⅳ (Diagnostic and Statistical Manual of Mental Disorders Ⅳ. American Psychiatric Association, 1994)[13]の診断基準で診断された統合失調症患者（34名）であり，本研究エントリー以前にさまざまな向精神薬による薬物療法では治療効果の乏しかった症例である。対象症例には抑肝散（2.5～7.5g/日）を4週間投与し，投与開始時，投与開始2週後および4週後に治療効果と副作用について，それぞれ評価尺度を用いて評価した。

2）臨床評価と安全性評価

精神症状の臨床評価としては，Positive and Negative Syndrome Scale（PANSS）[14]を用いた。また安全性評価として，抑肝散投与開始時および投与開始4週後に血液生化学検査を施行し，身体理学所見や自覚的副作用の有無を評価した。

PANSS：Positive and Negative Syndrome Scale

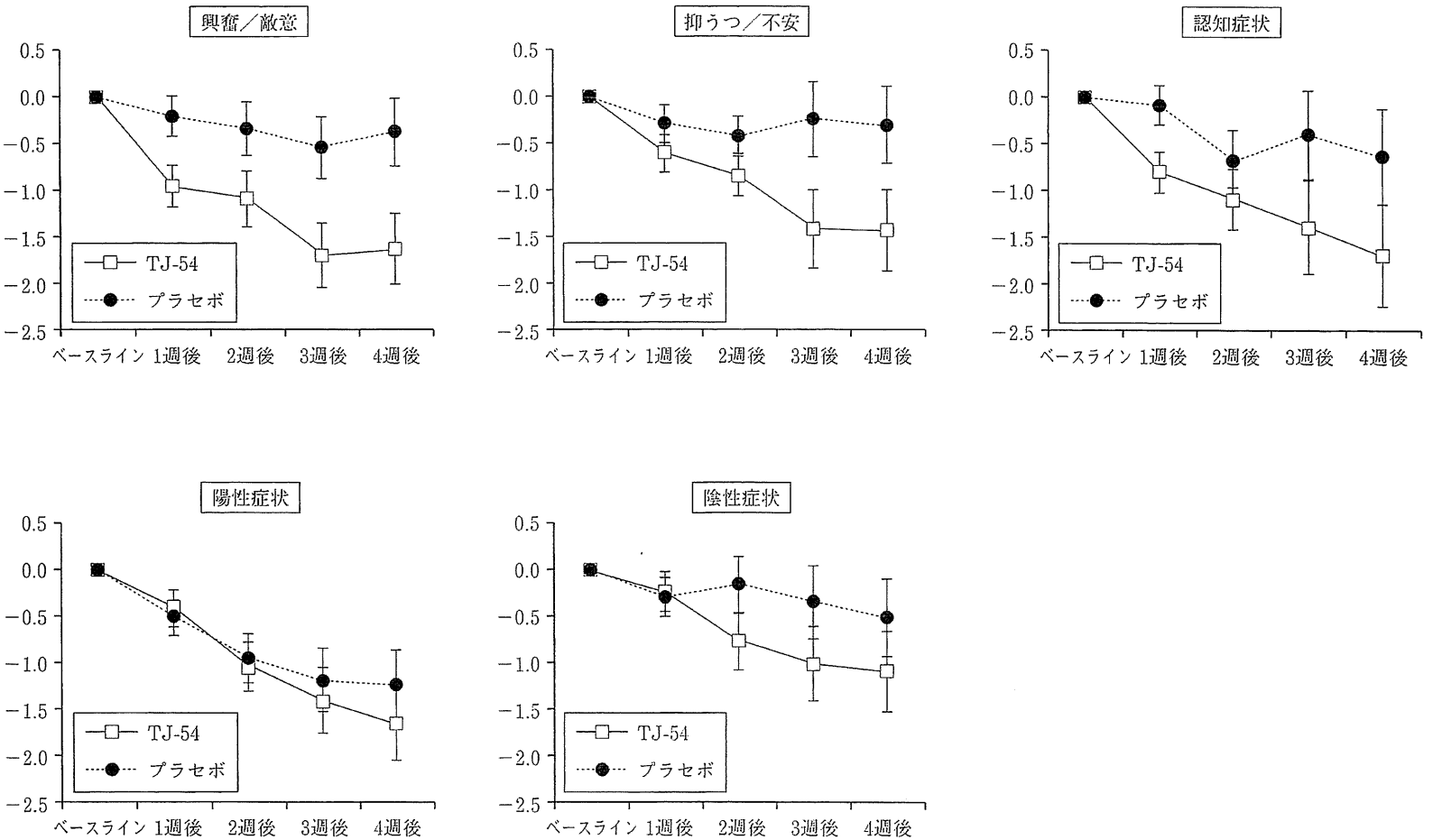

図4　PANSS 5 因子尺度の経時的変化

PANSS 5 因子のすべての尺度において，抑肝散投与群がより有効な傾向があった．統計的有意な改善を認めたのは興奮 / 敵意の尺度においてであった．

PANSS：Positive and Negative Syndrome Scale，TJ-54：抑肝散

（文献 11 より）

3）結果

本研究にエントリーした34名の患者がすべて4週間の研究期間を完了し，中止脱落症例はなかった。抑肝散の一日平均投与量は6.7±2.5g（2.5～7.5g）であった。臨床効果は，抑肝散の投与によりすべての評価尺度で有意な改善を認めた。そしてその治療効果は，いずれも抑肝散投与2週後に認められ，その効果は4週後まで持続した。特に幻覚妄想などの精神症状を中心とするpositive symptom subscaleにおける改善度が著明であった。（**図1**）。投与開始4週後に施行した血液生化学検査では異常検査値の発現は認めず，臨床上外覚的な有害事象もなく，自覚的な副作用としては頭痛が2症例，全身倦怠感が2症例で認められたが，軽微で一過性のものであった。

3．治療抵抗性統合失調症に対する抑肝散の有用性と安全性に関する多施設共同二重盲検ランダム化比較試験

本研究においては，治療抵抗性統合失調症の治療薬として抑肝散が有用であるかを無作為化二重盲検試験で検討することを目的とした。具体的にはプラセボを用いた，全国多施設共同の二重盲検ランダム群間比較対照試験にて抑肝散の有効性を客観的に評価した[11]。本研究の成果により，漢方医療のエビデンス創出法の範となるばかりでなく，統合失調症の治療抵抗化に伴う医療資源・コストの節減，頻回の入院や長期入院などによる患者とその家族の負担が軽減され，患者の社会復帰の可能性の向上が期待できると考えた。また，抗精神病薬の多剤大量処方を抑制し，その適正使用による医療経済的効果は極めて大きいと思われた。

1）対象と方法

対象症例はDSM-Ⅳ-TR（text revision）の診断基準で統合失調症と診断された治療抵抗性症例（抗精神病薬による治療にも関わらず6週間以上病状の改善が認められない症例で，文書による同意を取得できたもの）である[15]。また，試験デザインはプラセボとWEB登録方式を用いた，多施設共同・二重盲検無作為化群間比較対照試験とした。

実薬群を「標準的治療法に抑肝散を併用投与したもの」，プラセボ群を「標準的治療にプラセボ薬を併用投与したもの」の二群に分けた。投与期間は4週間とした。実薬群60例，プラセボ群60例の計120例を試験対象数として設定した。

2）臨床評価と安全性評価

精神症状の臨床評価としてはPANSSの5因子解析法を用いた[16]。（**図2**）。また安全性評価として，抑肝散投与開始時および投与開始4週後に血液生化学検査，理学検査を行い評価した。また自覚的副作用の有無も評価した。

3）結果

本研究にエントリーした120例の患者のうち全117例が4週間の研究期間を完了し（実薬群：56例，プラセボ群61例），中止脱落症例は3例であった。（プラセボ群：3例）。（**図3**）。臨床効果は**図4**で示すように，抑肝散の投与によりPANSSの5因子分類のすべてでプラセボと比較して，より強い改善傾向を認めた。統計学的にはPANSS-excitement/hostilityにおいてのみ，その改善効果は有意であった。投与開始4週後に施行

表1　安全性と忍容性

抑肝散投与による有害事象は認めなかった．

	TJ-54 (n = 56)	Placebo (n = 62)
Psychological	0	1
Neurological	0	0
Gastrointestinal	0	1
Genitourinary	0	0
Musculoskeletal	0	0
Dermatological	0	0
Respiratory	0	0
Cardiovascular	0	0
Infection	0	0
Ear, nose, and throat	0	0
Haematological	0	1
Endocrine	0	2
Other	0	0
Overall	0	5

TJ-54：抑肝散

（文献11より）

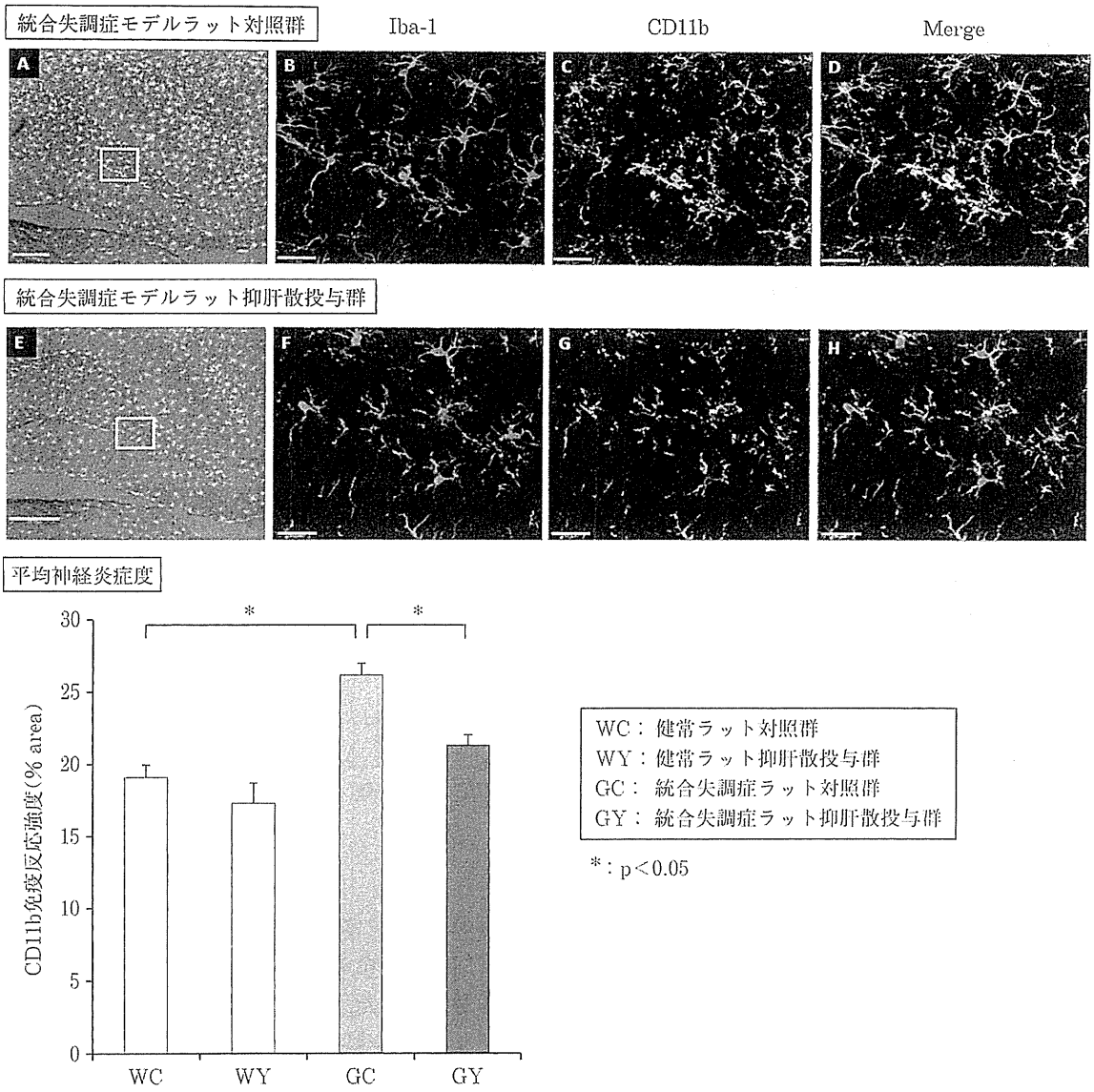

図5 抑肝散の抗神経炎症効果

抑肝散投与により，統合失調症ラットにおける過剰な神経炎症は，有意に抑制された．

（文献24より）

（本誌 p.10 カラーグラフィック頁参照）

した血液生化学検査では重度な異常検査値の発現は認めず，臨床上重篤な有害事象もなく，自覚的な副作用としては実薬群では認めず，プラセボ群では2症例で認められたが軽微なものであった。(表1)。

4．考 察

今回示した我々の研究結果により，抑肝散が治療抵抗性統合の治療において有用である可能性が示された。オープン試験については，プラセボ効果などのさまざまな研究結果に及ぼす要因の可能性を考慮する必要があり，研究結果の解釈は慎重である必要があった。そのため，さらに確かな高いエビデンスとなり得る結果を得るために，大規模二重盲検試験を実施した。その結果からも抑肝散の有用性が確認できた。

本研究において有意な効果を認めたのは，PANSSの5因子尺度のうちPANSS-excitement/hostilityの1因子尺度のみであった。他の尺度で統計的有意性を認めなかったのは，本試験が4週

間という短期間の臨床試験だったことによる可能性も考えられる。今後，さらに長期間の試験デザインでの検討が必要と思われた。しかし抑肝散が治療抵抗性統合失調症の治療において，高い有効性と忍容性を有することを初めて報告したものであり，今後の抑肝散の臨床研究の方向性を示す上で一定の意義があるものと考える。つまり治療抵抗性統合失調症の症例においては，精神運動興奮や敵意，猜疑心が強い場合，抑肝散が有効となる可能性を強く示唆するものである。

抑肝散には数種の生薬が含まれており，その治療効果の薬理学的作用機序について考察することは極めて困難である。しかしながら，抑肝散がGABA（γ-アミノ酪酸）作動性を有することや，グルタミン酸系ニューロンやセロトニン系ニューロンの神経伝達の安定性に寄与する可能性を示す報告もあり[17][18]，BPD患者の衝動性の亢進[19]，TDの症状形成[20]，統合失調症における治療抵抗性成立[12]のいずれにおいても，脳内のセロトニン代謝異常などが関与することが数多く報告されており，併せて考察すると非常に興味深い。

また近年，精神疾患における神経炎症仮説に関する研究成果が注目されている[21]。特にその中でも，脳内ミクログリアの活性の異常亢進が精神疾患の病態に関与している可能性が高いとされている[22]。

我々は統合失調症モデルラットにおいて，抑肝散が抗神経炎症作用を有する可能性を示唆することを報告した[23][24]。（**図5**）。脳組織学的検討では抑肝散が脳内ミクログリアの活性亢進を抑制する知見を得たが，さらに行動学的所見と関連していた。この知見は，同じく統合失調症の治療薬としての可能性が期待される塩酸ミノサイクリンに共通した作用機構を，抑肝散が有している可能性を示唆するものである[25][26]。抑肝散のさらに詳細かつ広範な脳内作用機序については，今後の基礎研究の進展も望まれる。

［謝辞］

本稿で紹介した共同研究にご協力いただいた研究分担者，試験担当者および試験参加施設職員の皆様に感謝申し上げます。

本稿で引用した研究は，平成22～24年（2010～2012年）度厚生労働科学研究費補助金（医療技術実用化総合研究事業）「治療抵抗性統合失調症に対する抑肝散の有用性と安全性に関する多施設共同二重盲検ランダム化比較試験」（研究代表者：堀口 淳）による助成を受けて実施された。

文　献

1) Aizawa R, Kanbayashi T, Saito Y, et al : Effects of yoku-kan-san-ka-chipi-hange on the sleep of normal healthy adult subjects. Psychiatry Clin Neurosci **56** : 303-304, 2002.
2) Iwasaki K, Satoh-Nakagawa T, Maruyama M : A randomized observer-blind, controlled trial of the traditional Chinese medicine Yi-Gan San for improvement of behavioral and psychological symptoms and activities of daily living in dementia patients. J Clin Psychiatry **66** : 248-252, 2005.
3) Jeste DV, Caligiuri MP, Paulsen JS : Risk of tardive dyskinesia in older patients : a prospective longitudinal study of 266 outpatients. Arch Gen Psychiatry **42** : 756-765, 1995.
4) Miyaoka T, Furuya M, Yasuda H, et al : Yi-gan san for treatment of borderline personality disorder : an open-label study. Prog Neuropsychopharm & Biol Psychiatry **32** : 150-154, 2008.
5) Miyaoka T, Furuya M, Yasuda H, et al : Yi-gan san for treatment of neuroleptic-induced tardive dyskinesia : an open-label study. Prog Neuropsychopharm & Biol Psychiatry **32** : 761-764, 2008.
6) Miyaoka T, Nagahama M, Tsuchie K, et al : Charles Bonnet syndrome : successful treatment of visual hallucinations due to vision loss with Yi-gan san. Prog Neuropsychopharm & Biol Psychiatry **33** : 382-383, 2009.
7) Miyaoka T, Wake R, Furuya M, et al : Yokukan-san (TJ-54) for treatment of very-late-onset schizophrenia-like psychosis : an open-label study. Phytomedicine **15** : 654-658, 2013.
8) Miyaoka T, Wake R, Furuya M, et al : Yokukan-san (TJ-54) for treatment of pervasive developmental disorder not otherwise specified and Asperger's disorder : a 12-week prospective,

open-label study. BMC Psychiatry **12** : 215, 2012.
9) Wake R, Miyaoka T, Inagaki T, et al : Yokukansan (TJ-54) for irritability associated with pervasive developmental disorder in children and adolescents : a 12-week prospective, open-label study. J Child Adolesc Psychopharmacol **23** : 329-336, 2013.
10) Miyaoka T, Furuya M, Yasuda H, et al : Yi-gan san as adjunctive therapy for treatment-resistant schizophrenia : an open-label study. Clin Neuropharmacol **32** : 6-9, 2009.
11) Miyaoka T, Furuya M, Horiguchi J, et al : Efficacy and Safety of Yokukansan (TJ-54) for Treatment-Resistant Schizophrenia : A Randomized, Multi-centre, Double-blind, Placebo-controlled Trial. Psychopharmacol **232** : 155-164, 2015.
12) Conley RR, Buchanan RV : Evaluation of treatment-resistant schizophrenia. Schizophr Bull **23** : 663-674, 1997.
13) American Psychiatrric Association : Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition. Washington, DC : American Psychiatric Association. 1994.
14) Kay SR, Fiszbein A, Opler LA : The positive and negative syndrome scale (PANSS) for schizophrenia. Schizophr Bull **13** : 261-276, 1987.
15) Kane JM, Honigfeld G, Singer J, et al : Clozapine in treatment-resistant schizophrenia. Psychopharmacol Bull **24** : 62-67, 1988.
16) Lindenmayer JP, Grochowski S, Hyman RB : Five factor model of schizophrenia : replication across samples. Schizophr Res **14** : 229-234, 1995.
17) Shimada Y, Goto H, Itoh T : Evaluation of the protective effects of alkaloids isolated from the hooks and stems of uncaria sinesis on glutamate-induced neuronal death in cultured cerebellar granule cells from rats. J Pharm Pharmcol **51** : 715-722, 1999.
18) Egashra N, Iwasaki K, Ishibashi A, et al : Repeated administration of yokukansan inhibits DOI-induced head-twitch response and decrease expression of 5-hydroxytryptamine (5-HT) 2A receptor in prefrontal cortex. Prog Neuropsychopharm & Biol Psychiatry **32** : 1516-1520, 2008.
19) Hansenne M, Pitchot W, Ansseau M : Serotonin, personality and borderline personality. Acta Neuropsychiatrica ; **14** : 66-70, 2002.
20) Seibyl JP, Glazer WM, Innis PB : Serotonin function in tardive dyskinesia. Psychiatr Annals **19** : 310-314, 1989.
21) Lin A, Kenis G, Bignotti S, et al : The inflammatory response system in treatment-resistant schizophrenia : Increased serum interleukin-6. Schizophr Res **32** : 9-15, 1998.
22) Doorduin J, de Vries EFJ, Willemsen ATM, et al : Neuroinflammation in schizophrenia-related psychosis : A PET study. J Nucl Med **50** : 1801-1807, 2009.
23) Liaury K, Miyaoka T, Tsumori T, et al : Morphological features of microglial cells in the hippocampal dentate gyrus of Gunn rat : A possible schizophrenia animal model. J Neuroinflammation **9** : 56, 2012.
24) Furuya M, Miyaoka T, Tsumori T, et al : Yokukansan promotes hippocampal neurogenesis associated with the suppression of activated microglia in Gunn rat. J Neuroinflammation **10** : 145, 2013.
25) Miyaoka T : Clinical potential of minocycline for schizophrenia. CNS Neurol Disord Drug Targets **7** : 376-381, 2008.
26) Liaury K, Miyaoka T, Tsumori T, et al : Minocycline improves recognition memory and attenuates microglial activation in Gunn rat : a possible hyperbilirubinemia-induced animal model of schizophrenia. Prog Neuropsychopharm & Biol Psychiatry **50** : 184-190, 2014.

Psychopharmacology (2015) 232:155–164
DOI 10.1007/s00213-014-3645-8

ORIGINAL INVESTIGATION

Efficacy and safety of yokukansan in treatment-resistant schizophrenia: a randomized, double-blind, placebo-controlled trial (a Positive and Negative Syndrome Scale, five-factor analysis)

Tsuyoshi Miyaoka · Motohide Furuya · Jun Horiguchi · Rei Wake · Sadayuki Hashioka · Masaya Tohyama · Norio Mori · Yoshio Minabe · Masaomi Iyo · Shyuichi Ueno · Sachiko Ezoe · Kenta Murotani · Syuzo Hoshino · Haruo Seno

Received: 3 September 2013 / Accepted: 30 May 2014 / Published online: 13 June 2014

Abstract
Background Treating schizophrenia patients who fail to respond to antipsychotics is a major challenge, and the percentage of treatment-resistant patients is estimated to be 20–25 %. Recent studies indicate that yokukansan (YKS; D2 and 5HT1A partial agonist and 5HT2A and glutamate antagonist) to be safe and useful in treating behavioral and psychological symptoms associated with dementia and other neuropsychiatric conditions. We aimed at evaluating both the efficacy and safety of YKS in patients with treatment-resistant schizophrenia.
Methods This randomized, multicenter, double-blind, placebo-controlled study was conducted between May 2010 and August 2012. One hundred twenty antipsychotic-treated inpatients from 34 psychiatric hospitals in Japan were included. Patients were randomized to adjuvant treatment with YKS 7.5 g/day or placebo. During a 4-week follow-up, psychopathology was assessed using the Positive and Negative Syndrome Scale (PANSS) with five factors [excitement/hostility (P4, P7, G8, and G14), depression/anxiety (G1, G2, G3, G4, and G6), cognition (P2, N5, N7, G5, G10, G11, G12, G13, and G15], positive (P1, P3, P5, P6, and G9), and negative (N1, N2, N3, N4, N6, G7, and G16]]. Other assessments included, Clinical Global Impression—Severity (CGI-S), Global Assessment of Functioning (GAF), and Drug-Induced Extrapyramidal Symptoms Scale (DIEPSS). The primary efficacy outcome was the change in PANSS five-factor scores. The secondary outcomes were changes in the scores of

Trial registration: controlled-trials.com identifier: UMIN000005018

T. Miyaoka (✉) · M. Furuya · J. Horiguchi · R. Wake · S. Hashioka
Department of Psychiatry, Shimane University School of Medicine, Izumo, Japan
e-mail: miyanyan@med.shimane-u.ac.jp

M. Tohyama
Research Institute of Traditional Asian Medicine, Kinki University, Higashi-Osaka, Japan

N. Mori
Department of Psychiatry and Neurology, Hamamatsu University School of Medicine, Hamamatsu, Japan

Y. Minabe
Department of Psychiatry, Kanazawa University School of Medicine, Kanazawa, Japan

M. Iyo
Department of Psychiatry, Chiba University School of Medicine, Chiba, Japan

S. Ueno
Department of Psychiatry, Ehime University School of Medicine, Matsuyama, Japan

S. Ezoe
Medical Center for Translational Research, Osaka University Hospital, Suita, Japan

K. Murotani
Center for Advance Medicine and Clinical Research, Nagoya University Hospital, Nagoya, Japan

S. Hoshino
Department of Psychiatry, Takeda General Hospital, Fukushima, Japan

H. Seno
Department of Psychiatry, Matsue Aoba Hospital, Matsue, Japan

CGI-S. The analysis was made on a modified intention to treat basis with the help of a last observation carried forward method.

Results YKS showed a tendency of superiority to placebo in reducing total all PANSS five-factor scores in treatment-resistant schizophrenia, but the difference was not statistically significant in total, depression/anxiety, cognition, positive, and negative factors. However, compared to the placebo group, the YKS group showed statistically significant improvements in the PANSS excitement/hostility factor scores ($p<0.05$). No substantial side effects were recorded.

Conclusion The results of the present study indicate YKS to be a potential adjunctive treatment strategy for treatment-resistant schizophrenia, particularly to improve excitement/hostility symptoms.

Keywords Schizophrenia

Introduction

Treating patients with schizophrenia who either respond minimally to treatment or do not respond at all represents a major clinical challenge. Patients resistant to antipsychotic treatment constitute up to 20–25 % of all patients with schizophrenia (Conley and Buchanan 1997). Despite the introduction of atypical antipsychotics for treatment-resistant schizophrenia, clinicians are faced with the challenge of treating patients with drug-resistant schizophrenia (Taylor et al. 2003; Howes et al. 2012). A majority of these individuals experience negative symptoms that account for a significant impact on morbidity and diminished quality of life associated with chronic forms of schizophrenia. In such situations, alternative therapeutic approaches involving a combination of standard antipsychotic treatment with other drugs are employed. However, only a handful of adjunctive treatment options have been systematically studied in clinical settings. Adjunctive therapies can result in polypharmacy and therefore require careful monitoring of any of its associated events. It was reported that patients with schizophrenia whose illness is resistant to antipsychotic treatment have relatively normal levels of dopamine synthesis capacity, compared with levels in patients whose symptoms respond to treatment. This suggests either that patients with treatment-resistant illness start with a different underlying pathophysiology or that antipsychotics have an effect on their dopamine synthesis capacity, albeit one that does not reduce symptoms (Demijaha et al. 2012).

Yokukansan (Yi-gan san; TJ-54; YKS) was developed in 1555 as a remedy for restlessness and agitation in children (Aizawa et al. 2002). Prompted by the increasing life expectancy of the Japanese population, geriatricians have begun to use this traditional treatment for behavioral and psychological symptoms of dementia (BPSD) in the elderly. For example, Tahara et al. reported successful YKS treatment of two patients with BPSD in an extended care unit (Tahara et al. 2003). Iwasaki et al. reported that YKS improved hallucination and delusion in dementia with Lewy bodies (Iwasaki et al. 2005a). Moreover, in a randomized, observer-blind, controlled trial, YKS improved BPSD and activities of daily life (Iwasaki et al. 2005b). Furthermore, in a previous open-label study, we reported YKS therapy to be an effective and a well-tolerated option for several neuropsychiatric disorders, namely borderline personality disorder, drug-induced tardive dyskinesia, treatment-resistant schizophrenia, late-onset schizophrenia, visual hallucinations due to vision loss, and pervasive developmental disorder (Miyaoka et al. 2008a, b, 2009a, b, 2011, 2012, 2013; Miyaoka and Horiguchi 2009; Wake et al. 2013). Clinical trials and detailed case reports of YKS (Mizukami et al. 2009; Monji et al. 2009; Kawanabe et al. 2010; Okahara et al. 2010; Hayashi et al. 2010; Kimura et al. 2010; Iwasaki et al. 2011, 2012; Sumiyoshi et al. 2011; Nakata et al. 2012; Kajitani and Kanba 2012) suggest the possibility of it representing a new treatment approach for treatment-resistant schizophrenia. YKS extract is a herbal medicine containing the rhizome of *Atractylodes lancea* [Japanese Pharmacopoeia (JP)], sclerotium of *Poria* (JP), *Cnidium rhizome* (JP), hook of *Uncaria* (JP), root of Japanese andgelia (JP), root of *Bupleurum* (JP), and *Glycyr rhiza* (JP). YKS has been used for the treatment of insomnia, irritability, and convulsions for many years, and the pharmacological effects of YKS are thought to be associated with 5-hydroxytryptamine (5-HT) receptors (Tahara et al. 2003; Iwasaki et al. 2005b).

This study aimed to evaluate the efficacy and tolerability of YKS as an add-on pharmacotherapy for clinical symptoms in patients with treatment-resistant schizophrenia over a 4-week period. We hypothesized that YKS would reduce some symptoms of treatment schizophrenia and consequently result in improved social and global functioning. To the best of our knowledge, no double-blind, placebo-controlled trials have been performed to examine the clinical efficacy of YKS as an adjunctive to antipsychotic therapy for the treatment of treatment-resistant schizophrenia.

Materials and methods

Materials

YKS extract was provided by Tsumura & Co. (Tokyo, Japan). YKS is a mixture of dried herbs containing 4 g of the rhizome of *A. lancea*, 4 g of *Poria*, 3 g of C. *rhizome*, 3 g of *Angelicae radix* (*Angelica acutiloba*), 2 g of *Bupleuti radix*, 1.5 g of *Glycyrrhizae radix*, and 3 g of *Uncariae uncis cum ramulus*. These herbs are registered in the JP (ver. 15) (The Ministry of Health, Labor, and Welfare 2006). The amount of active ingredients in the powder extract has been found to be

equivalent to that in the standard solution of individual components as confirmed by thin-layer chromatography. Manufacturing processes and quality control measures were in conformance with good manufacturing practices. YKS has been approved by the Ministry of Health, Labor, and Welfare and covered by the National Health Insurance plan. The compounds on the chromatogram were classified on the basis of the constituent herbs of YKS (Table 1; Nakata et al. 2012).

Study participants

The study involved inpatients from 34 psychiatric hospitals in Japan. On the basis of data from previous reports, we calculated the required sample size to be 49 with an α-error of 0.05 and power of 0.9 (Miyaoka et al. 2009a; Stern et al. 1997). The protocol was approved by the Shimane University School of Medicine Subjects Review Committee and carried out in accordance with the Declaration of Helsinki, with written informed consent obtained from all recruited subjects.

Treatment-resistant schizophrenia was defined as little or no response to treatment from at least two adequately dosed antipsychotic trials for at least 4 weeks including at least one second-generation antipsychotic (>600 mg/day of chlorpromazine equivalent), the presence of persistent positive psychotic symptoms characterized by PANSS scores of 4 or higher on at least two items from the positive subscale, a PANSS total score >60, and CGI >4; constructs were adopted from the US multicenter trial of clozapine (Kane et al. 1988).

Male or female hospitalized patients were eligible for inclusion in the study if they met all of the following criteria: age of 20–59 years old, a primary Diagnostic and Statistical Manual of Mental Disorders, fourth edition, text revision (DSM-IV-TR) (American Psychiatric Association 2000) diagnosis of schizophrenia, established by the Structured Clinical Interview for Diagnostic and Statistical Manual of Mental Disorders, fourth edition, (SCID) (First 1995), with a length of at least 3 years, history of documented treatment-resistant status, which is defined as the absence of clinically significant improvement after treatment with at least two neuroleptics for 6 weeks or longer after receiving a full dose equivalent to 600 mg/day of chlorpromazine, presence of persistent positive symptoms as evidenced by a score of at least 10 on the positive symptom subscale of the Positive and Negative Syndrome Scale (PANSS) (Kay et al. 1987), and an overall score of at least 60 on the PANSS and ≥4 (moderately ill) on the Clinical Global Impression-Severity (CGI-S) (Guy 1976). The current episode period is at least 6 weeks at the screening examination to exclude patients with acute phase. Exclusion criteria included pregnancy, lactation, other clinical significant or unstable conditions, and history of alcohol or substance abuse in the last 6 months. No patients had been not treated by clozapine in this clinical trial.

Study design

The study was a 4-week, double-blind, placebo-controlled, fixed-flexible dose trial. Treatment allocation was concealed from the study participants and the physicians who rated them using sequentially numbered, opaque, and sealed envelopes. Random allocation and clinical assessment of the participants were done by separate persons. Physical examination and routine laboratory test including evaluation of prolactin were carried out at baseline. Existing medications at baseline remained unchanged, whereas initiation of other psychotropic medications was not permitted during the trial. Patient status was reviewed every week by evaluation of clinical outcomes and vital signs (blood pressure and pulse rate). Subsequently, the dosettes were reviewed, and medication was dispensed for the following week.

Medication

Subjects were randomized to receive either YKS or placebo (1:1). The active drug and the placebo were constituted in a powder form, which was identified by a company specializing in the preparation of drug for experimental trials (Tsumura & Co.).

Study participants in the test group received 2.5 g of YKS powder three times a day for weeks. Study medication was dispensed in dosettes, and the drug package counts were determined at each visit to monitor adherence.

Patients continued their regular antipsychotic treatment. Psychiatrists were requested to delay any changes in antipsychotic treatment until after trial to keep the dose of underlying antipsychotics constant.

Clinical measurements

Assessments included evaluation of clinical response and adverse effects. Clinical responsiveness was evaluated with the help of PANSS five-factor (excitement/hostility [P4, P7,.G8, and G14], depression/anxiety [G1, G2, G3, G4, and G6], cognition [P2, N5, N7, G5, G10, G11, G12, G13, and G15], positive [P1, P3, P5, P6, and G9], and negative [N1, N2, N3, N4, N6, G7, and G16]) (Lindenmayer et al. 1995; Citrone et al. 2011), CGI-S, and Global Assessment of Functioning (GAF) (Guy 1976). Global adverse effects and movement disorder were evaluated for assessing tolerability. Movement disorder was evaluated with the help of Drug-Induced Extrapyramidal Symptom Scale (DIEPSS) (Inada et al. 2009). Efficacy and tolerability scores were evaluated by the principal investigator. The primary outcome measure was change in PANSS five-factor scores. Secondary outcomes were changes in CGI-S. The patients, the clinician who referred them, the psychiatrist who rated the participants and prescribed the medication, and the statistician were blind to allocation.

Table 1 Classification of the compounds identified in the three-dimensional chromatogram

Constituent of YKS	Compounds
Atractyloids lanceae rhizome	4E,6E,12E-Tetradecatriene-8,10-diyne-1,3,14-triol,
	12-isovaleroyl-2E,8E,10E-triene-4,6-diyne-1,14-diol
	14-isovaleroyl-2E,8E,10E-triene-4,6-diyne-1,12-diol, atractylodin
Cnidii rhizoma	Ferulic acid, ligustilide
Uncariae uncis cum ramulus	Geissoschizine methyl ether, hirsuterine, hirsutine
Angelicae radix (Angelica acutiloba)	Xanthotoxin, ligustilide
Bupleuti radix	Saikosaponin b1, saikosaponin b2
Glycyrrhizae radix	Formononetin, formononetin-7-*O*-glucoside
	Liquiritigenin, liquiritin, liquiritin apioside, glycyrrhizin, glycyroside, isoliquiritin apioside
	Isoliquiritin, isoliquiritigenin, glycylcoumarin

Statistical analysis

Analyses were performed on a modified intention to treat (mITT). mITT includes data from all patients who were randomly assigned to a treatment group and who received at least one dose of study medication and one of assessments. If a patient dropped out, all outcome measures were assessed within a week. We first examined baseline differences between the randomized groups.

To assess the efficacy of YKS, we used linear mixed models for fixed and random effects with the dependent variable being the PANSS five-factor scores. Time and group were entered as a continuous and dichotomous independent variable, respectively. The 4-week treatment efficacy of YKS compared to placebo for each outcome was estimated by entering a group-by-time interaction term. Mixed models are superior for the analysis of longitudinally correlated data with missing values (Gibbons et al. 1993). These models make use of all available data and consequently have the best statistical power. Dependency of repeated assessments of the outcome scores was taken into account by including random effects for patients with an unstructured variance-covariance structure. Model-estimated marginal means for each follow-up visit were calculated according to treatment group. In addition, we performed a more conservative analysis of the PANSS five-factor scores with the help of the last observation carried forward (LOCF) method for those who dropped out of the study during follow-up. In these analyses, differences in score changes between the randomized groups were evaluated using the unpaired t test.

Analyses, blind to treatment status, were performed using the Statistical Analysis System (SAS) statistical package (SAS Institute Inc., Cary, North Carolina). The two-sided level of significance was set at 0.05. Values are reported as mean with corresponding 95 % confidence intervals (CIs) wherever appropriate.

Results

Subject demography, clinical characteristics, and follow-up

In total, of the 136 participants initially screened, 122 were found eligible to participate, and of these, 120 elected to take part in the trial. One hundred twenty patients treated with antipsychotics were included in the run-in period (Fig. 1). Of these 120 patients, 120 were eligible and were randomly assigned. Baseline characteristics are shown in Table 2. The percentage of the men in the placebo group was slightly higher than in the YKS group; however, the difference was not significant. Other baseline characteristics showed no material differences. No significant difference was present between the groups in receiving antipsychotics (chlorpromazine equivalent; mean=2,037.2±2,046.8 mg/day in the YKS group and 1,925.8±2,040.2 mg/day in the placebo group, respectively). Notably, the scores of the PANSS five-factor subscales were comparable between the two randomized groups. Three patients (4.7 %) in the placebo group did not complete follow-up. The principal reasons for dropouts and missing data were a disinterest in participation (n=2) and medical conditions (n=1). The average compliance from randomization to the last follow-up was estimated by package count and was found to be 99 % in the YKS group and 100 % in the placebo group. The patients were enrolled between May 2011 and August 2012. Follow-up ended in December 2012.

Psychopathology

Group-specific model-estimated marginal means of the PANSS five-factor scores at each follow-up visit are shown in Fig. 2. The figure shows that decreases in scores of PANSS five-factor subscales with time were more pronounced in the YKS group than in the placebo group, more so with respect to the PANSS excitement/hostility subscale scores. Table 3 shows mean change in the total PANSS and PANSS five-factor scores from baseline to the last follow-up (LOCF)

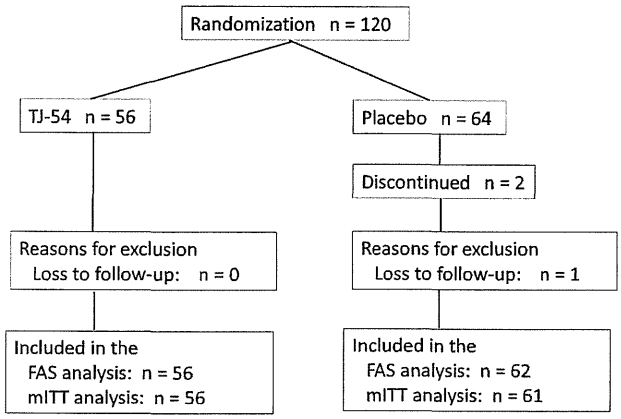

Fig. 1 Study design and patient flow chart

according to treatment group and estimates of treatment efficacy. Mixed models showed larger mean decreases in the YKS group than in the placebo group; however, there was no statistical difference in the total PANSS score and PANSS subscale score for depression/anxiety, cognition, positive, and negative symptoms between the group. The group-specific model-estimated marginal means of the PANSS subscale score for excitement/hostility at each follow-up visit are shown in Fig. 2. This parameter improved significantly with YKS than with placebo. Mixed models demonstrated larger decreases in the YKS group than in the placebo group, with statistically significant differences in the scores for excitement/hostility (Table 3). By sensitivity analysis, there is no difference between data of LOCF and observed cases (data not shown).

Safety and tolerability

To establish safety and tolerability of YKS, full analysis set (FAS) testing was performed. Treatment with YKS was well tolerated. Discontinuation from the study because of an adverse event was not observed (Fig. 1; Table 3). There were no statistically significant time or group×time interaction effects for DIEPSS (Table 2). There were no clinically relevant changes from baseline in terms of body weight, laboratory evaluations, vital signs, or QTc interval in either group.

Discussion

This is the first double-blind, placebo-controlled investigation of the therapeutic value of YKS in the treatment of psychotic disorders. The study results confirm that YKS can be used as an adjunctive to conventional therapy as it has positive effects on treatment-resistant schizophrenia, particularly by controlling excitement/hostility. The clozapine has not been available in Japan until 2009. Therefore, it might have been difficult to include patients who had undergone clozapine trial in the past.

Table 2 Baseline characteristics

	YKS (n=56)	Placebo (n=61)	Test statics
Age (years)	46.7±9.8	46.3±9.6	Ns
Gender (male/female)	34/22	39/22	Ns
Duration of disease (years)	24.0±10.4	23.6±10.2	Ns
Duration of treatment (years)	22.5±11.0	21.1±10.6	Ns
CPZ equivalents (mg)	2,037.2±2046.8	1,925.8±2,040.2	Ns
Type			
Paranoid	45	42	
Catatonic	6	8	
Undifferentiated	5	11	Ns
PANSS (excitement/hostility)	14.6±4.1	13.1±4.7	Ns
PANSS (depression/anxiety)	16.0±5.3	14.9±4.3	Ns
PANSS (cognition)	33.8±7.7	34.7±8.8	Ns
PANSS (positive)	21.6±4.2	22.4±4.6	Ns
PANSS (negative)	27.3±7.3	27.1±6.6	Ns
CGI-S	5.4±0.8	5.5±0.8	Ns
GAF	27.4±7.5	27.2±6.4	Ns
DIEPSS	4.3±4.0	4.8±4.3	Ns

CPZ chlorpromazine, *PANSS* Positive and Negative Syndrome Scale, *CGI-S* Clinical Global Impression—Severity, *GAF* Global Assessment of Functioning, *DIEPSS* Drug-Induced Extrapyramidal Symptoms Scale